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More Risk Information for Better Decisions

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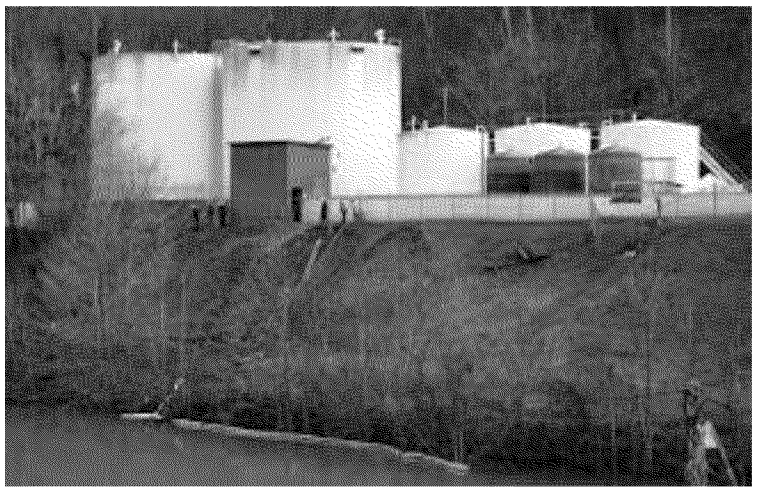
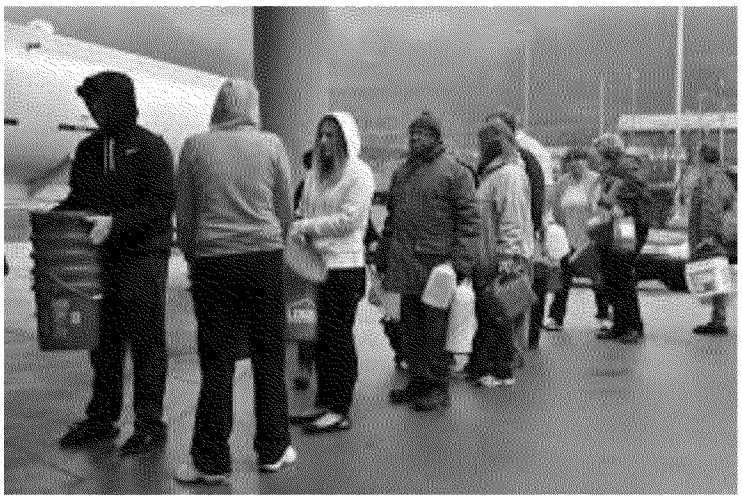
Elk River, WV Spill





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We Don't Know!

- "A little-known toxic chemical with a tongue-twisting name…." ""There are so many gaps on toxicity ... no one can say with acceptable certainty what a safe level is," says Daniel Horowitz, managing director of the U.S. Chemical Safety Board, which is investigating the leak." *USA Today* Chemical Spill Exposes Huge Gaps in Oversight: Our View

- Only U.S. Chemical Safety Board Chairman Rafael Moure-Eraso seemed to really want to try to wade into those issues. "It would be hard to say if it's safe," Moure-Eraso said. "In order to give a scientific answer, you have to have scientific information." *Charleston Gazette* Hearing provides few answers on water safety.

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My Cowardly Week

- Not returning phone calls from reporters
- Ducking the School of Public Health Communications Director
- Not helping with public understanding of a toxicology and risk issue

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What is the Result?

- Loss of confidence in regulatory system
- Loss of confidence in the chemical industry
- Calls for extreme measures in response
- Lawsuits

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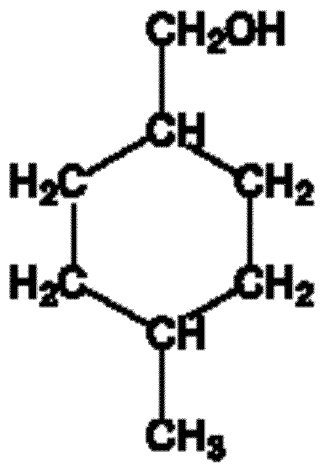
In Reality, We Know a Lot!

- 4-Methylcyclohexanemethanol
- CAS 34885-03-5
- Rat oral LD_{50} of 825 mg/kg
- Rat dermal LD_{50} of > 2000 mg/kg



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First, Acute Toxicity

- LD_{50} = 825 mg/kg/day

- Would be in Global Harmonized System (GHS) Category 4

ACUTE ORAL TOXICITY – Annex 1					
	Category 1	Category 2	Category 3	Category 4	Category 5
LD_{50}	≤ 5 mg/kg	> 5 < 50 mg/kg	≥ 50 < 300 mg/kg	≥ 300 < 2000 mg/kg	≥ 2000 < 5000 mg/kg
Pictogram					No symbol
Signal word	Danger	Danger	Danger	Warning	Warning
Hazard statement	Fatal if swallowed	Fatal if swallowed	Toxic if swallowed	Harmful if swallowed	May be harmful if swallowed

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What About Chronic Effects?

- What would we need to communicate and make decisions appropriately?
- Non-cancer — What would be an RfD?
- Carcinogenicity — What would be a 10^{-6} Virtually Safe Dose (VSD)?
- No chronic tests at this point

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Estimating an RfD

- Numerous studies have investigated the relationship between acute toxicity and non-cancer risk values
- All are approximate – some find stronger relationship than others

Regul Toxicol Pharmacol. 1987 Mar;7(1):96-112.

Deriving allowable daily intakes for systemic toxicants lacking chronic toxicity data.

Layton DW, Mallon BJ, Rosenblatt DH, Small MJ.

Abstract

The lack of human toxicological data for most chemical compounds makes it difficult to quickly assess health risks associated with exposure to contaminants at hazardous waste sites. It would therefore be advantageous to have a technique for estimating acceptable daily intakes (ADIs) of potentially toxic substances based on more widely available animal toxicity data. This article focuses on the use of LD50 data to derive provisional ADIs, and it suggests multiplying oral LD50 values (expressed in mg/kg of body wt) by a factor in the range of 5 X 10(-6) to 1 X 10(-5) day-1 to convert them to such ADIs. It is emphasized that these interim ADI values are no substitute for toxicity testing, but that such testing would most likely result in higher ADI estimates.

PMID: 3575800 [PubMed - indexed for MEDLINE]

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Estimating an RfD

- These relationships use very well tested chemicals
- Type of toxicity doesn't matter – RfDs usually set on most sensitive species/strain/sex/endpoint
- Can also reflect uncertainty due to range of ratios of LD_{50} (or similar) to RfD

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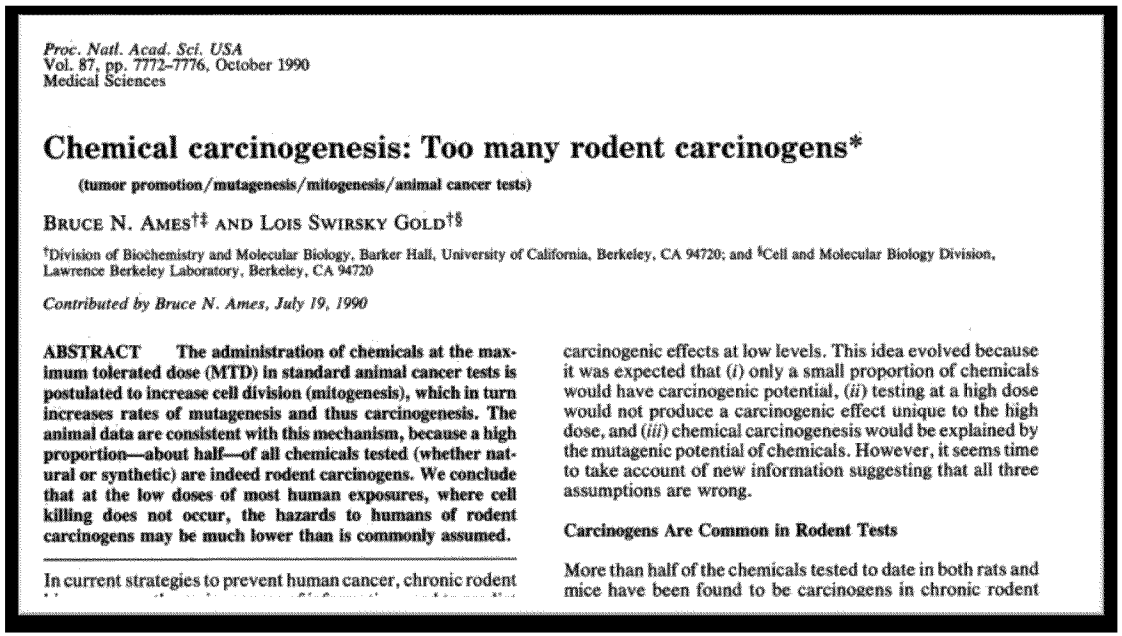
What About Cancer Risk?

- We know that 50% of all chemicals tested in long-term rodent bioassays are judged to be carcinogenic

- Some believe knowledge of mutagenicity may help judge carcinogenic potential



Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 7772–7776, October 1990
Medical Sciences

Chemical carcinogenesis: Too many rodent carcinogens*

(tumor promotion/mutagenesis/mitogenesis/animal cancer tests)

BRUCE N. AMES†‡ AND LOIS SWIRSKY GOLD†§

†Division of Biochemistry and Molecular Biology, Barker Hall, University of California, Berkeley, CA 94720; and §Cell and Molecular Biology Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720

Contributed by Bruce N. Ames, July 19, 1990

ABSTRACT **The administration of chemicals at the maximum tolerated dose (MTD) in standard animal cancer tests is postulated to increase cell division (mitogenesis), which in turn increases rates of mutagenesis and thus carcinogenesis. The animal data are consistent with this mechanism, because a high proportion—about half—of all chemicals tested (whether natural or synthetic) are indeed rodent carcinogens. We conclude that at the low doses of most human exposures, where cell killing does not occur, the hazards to humans of rodent carcinogens may be much lower than is commonly assumed.**

In current strategies to prevent human cancer, chronic rodent

carcinogenic effects at low levels. This idea evolved because it was expected that (*i*) only a small proportion of chemicals would have carcinogenic potential, (*ii*) testing at a high dose would not produce a carcinogenic effect unique to the high dose, and (*iii*) chemical carcinogenesis would be explained by the mutagenic potential of chemicals. However, it seems time to take account of new information suggesting that all three assumptions are wrong.

Carcinogens Are Common in Rodent Tests

More than half of the chemicals tested to date in both rats and mice have been found to be carcinogens in chronic rodent

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MCHM Mutagenicity

Predicted Mutagenicity for 34885-03-5 from Consensus method

Prediction results

Endpoint	Experimental value	Predicted value
Mutagenicity value	N/A	0.23
Mutagenicity result	N/A	Mutagenicity Negative

Individual Predictions

Method	Predicted value
Hierarchical clustering	0.25
FDA	0.12
Nearest neighbor	0.33

Source: EPA Toxicity Estimation Software Tool (http://www.epa.gov/nrmrl/std/qsar/qsar.html)

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Calculating Regulatory Risk Values

Risk Analysis, Vol. 11, No. 3, 1991

Estimation of Maximum Tolerated Dose for Long-Term Bioassays from Acute Lethal Dose and Structure by QSAR

Vijay K. Gombar,[1] Kurt Enslein,[1] Jeffrey B. Hart,[1] Benjamin W. Blake,[1] and Harold H. Borgstedt[1]

Received May 17, 1990; revised September 10, 1990

Risk Analysis, Vol. 24, No. 6, 2004

Tiered Chemical Testing: A Value of Information Approach

Fumie Yokota,[1] George Gray,[2] James K. Hammitt,[2] and Kimberly M. Thompson[2]*

REGULATORY TOXICOLOGY AND PHARMACOLOGY **28**, 222–225 (1998)
ARTICLE NO. RT981258

Regulatory Cancer Risk Assessment Based on a Quick Estimate of a Benchmark Dose Derived from the Maximum Tolerated Dose[1]

David W. Gaylor* and Lois Swirsky Gold†

**National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, Arkansas 72079; and †Lawrence Berkeley National Laboratory and University of California at Berkeley, Berkeley, California 94720*

Received February 9, 1998

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LD50 to MTD*

- Ratio of MTD/LD_{50} (K) is lognormally distributed
  - μ_{lnK} = -2.3
  - $sigma_{lnK}$ = 1.4
- MCHM LD_{50} = 825 mg/kg/day
- Central estimate of MTD is 220 mg/kg/day

* From Gombar *et al*. via Yokota *et al*.

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MTD to RfD*

- MTD to Benchmark Dose ($BMDL_{10}$)
  - $BMDL_{10}$ = MTD/7
  - MCHM = 220/7 = 31 mg/kg/day

- BMDL10 to RfD
  - RfD = $BMDL_{10}$/UF
  - MCHM = 31/1000# = **0.031 mg/kg/day**

*From Gaylor and Gold
#Gaylor and Gold suggest UF of 1000 assuming $BMDL_{10}$ is equivalent to a LOAEL

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$BMDL_{10}$ to Virtually Safe Dose

- Gaylor and Gold give relationship between $BMDL_{10}$ and doses at specific risk levels
  - Risk < 10^{-6} MTD/700,000
  - Risk < 10^{-5} MTD/70,000
  - Risk < 10^{-4} MTD/7,000

- MCHM 10^{-6} VSD 220/700,000 = **0.00004 mg/kg/day**

*From Gaylor and Gold

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Now I Have Risk Values

- Non-cancer:

  RfD = 0.031 mg/kg/day (31 µg/kg/day)

- Cancer (if it is a carcinogen)

  10^{-6} VSD = 0.00004 mg/kg/day (0.04 µg/kg/day)

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What About Exposure?

- Assume exposure through drinking water
  - Remember difference between oral and dermal LD_{50} – not well absorbed
  - Can adjust for other sources if necessary
- Make standard assumptions of 2L/day of water consumption and 70 kg body weight
- Remember chronic risk values should be compared to average lifetime daily dose – not single day exposure – so time matters

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Intakes at Different Levels of Water Contamination

PPM (µg/L)	Intake (L)	Body Weight (kg)	Dose (µg/kg/day)	
0.1	2	70	0.003	
1	2	70	0.029	
2	2	70	0.057	< VSD = 0.04
3	2	70	0.086	
4	2	70	0.114	
5	2	70	0.143	
10	2	70	0.286	
100	2	70	2.857	
1000	2	70	28.571	
10000	2	70	285.71	< RfD = 31

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What I Should Have Said

- We have some information on methylcyclohexanemethanol to help understand if it is an immediate danger
- Its acute toxicity is low – less toxic than caffeine or aspirin
- International standards would put it in Category 4 (out of 5) in the Globally Harmonized System for acute toxicity with a signal word of "Warning" rather than the "Danger" in higher categories
- It is difficult to imagine water levels could possible get high enough to pose a threat of acute toxicity

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What I Should Have Said

- We do not have long term toxicity data on MCHM specifically but, based on many years of experience with many other chemicals, we can estimate a risk value similar to that EPA would calculate if data were available

- The best estimate of that risk value is 31 µg/kg/day

- That means that as long as MCHM concentrations are below about 1000 ppm drinking the water – even every day for a lifetime – should not cause adverse effects

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What I Should Have Said

- We don't know if MCHM has the potential to be a carcinogen in standard tests – but 50% of all chemicals tested are positive

- Comparing MCHM's chemical structure to well tested chemicals suggests it would not interact with DNA to cause mutations – a property that would lead scientists to be more concerned about cancer potential

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What I Should Have Said

- Based on many years of experience with many other chemicals, we can estimate a risk value similar to that EPA would calculate if MCHM did give a positive result in a carcinogenicity test

- The level that would lead to what is generally considered a negligible risk is 0.04 µg/kg/day

- This means that drinking water with less than 1 ppm of MCHM, even every day for a lifetime, would not pose a significant cancer risk – and remember, that is assuming the chemical has carcinogenic potential

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Who Would Have Objected?

- Toxicologists – you don't have chemical specific toxicity information!
- Environmentalists – haven't tested every endpoint and lifestage!
- Industry – how can you say it might be a carcinogen without complete data set (and what about WOE and MOA)!
- Lawyers!

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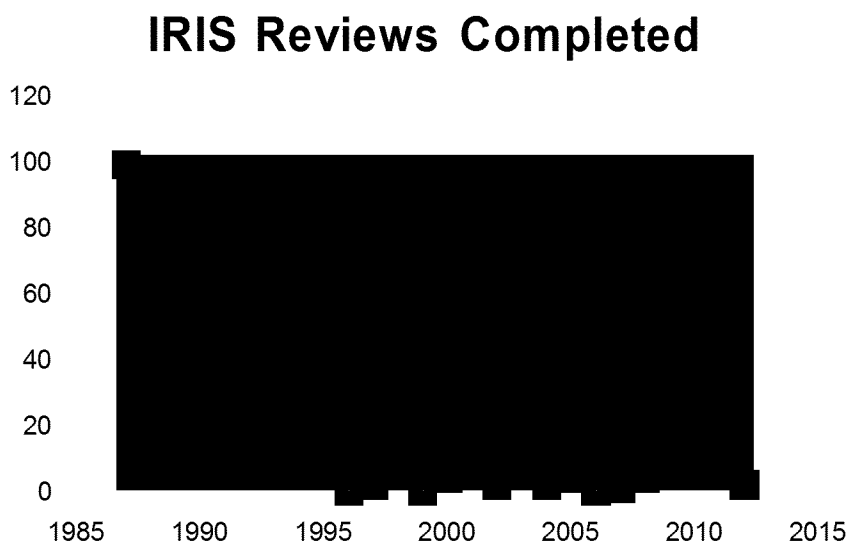
We Can't Go On Like This

- Testing is expensive and slow
- Assessment is slow and contentious
- Inhibit technological advances
- Loss of public confidence



http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction =iris.showSubstanceList&list_type =date&view =all

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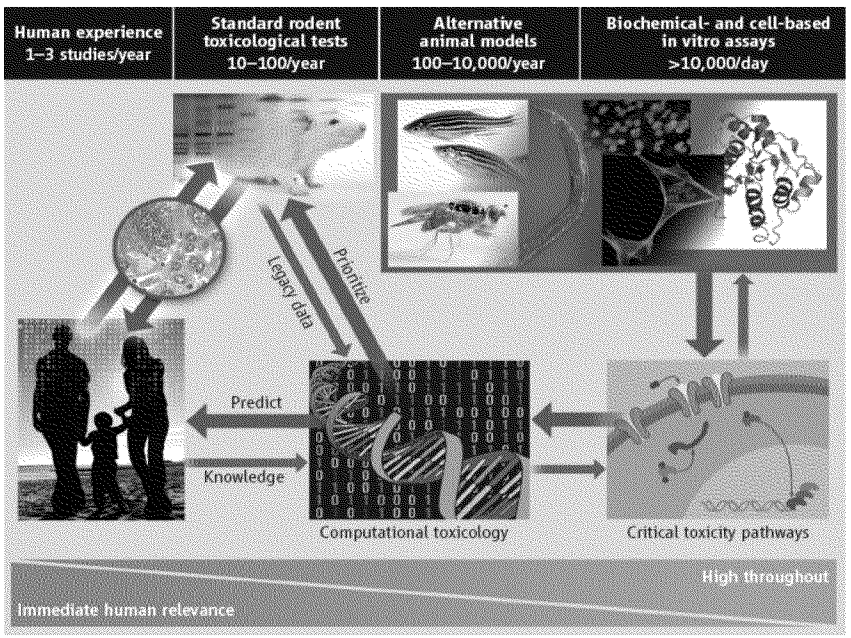
What About Tox21?

- Can't yet turn into risk values to compare to exposure
- Always another assay to do – when do we know enough to say something?
- Could help define "below x should not be a problem" if we can agree on which outcomes in which assays matter



Source: Collins, F.S., Gray, G.M., Bucher, J.R. (2008) Toxicology. Transforming Environmental Health Protection. *Science* **319**:906-7

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What to Do?

- Remember our goal is making appropriate chemical use decisions
- Risk-based decisions require quantitative risk values
- In many cases we have significant toxicologic information (more than MCHM) but no risk numbers
- Need way to develop “rough and ready” risk values

COMMENT

ARCHITECTURE The Victorian woman who celebrated nature in stone p.28 | MUSEUMS Mathematician Glen Whitney talks about founding MoMath p.32 | SANITATION A call to stop India's trains spreading disease across the subcontinent p.33 | OBITUARY Martin Fleischmann, electrochemist in cold fusion furore, remembered p.34

The town of Times Beach in Missouri was evacuated in 1983 and later demolished after a dioxin spill.

Rethink chemical risk assessments

The US Environmental Protection Agency needs to speed up its risk analyses and address uncertainty, say **George M. Gray** and **Joshua T. Cohen**.

The US Environmental Protection Agency (EPA) is under fire. Its flagship Integrated Risk Information System (IRIS), which develops risk values for

Last year, for instance, the US National Academy of Sciences (NAS) castigated the EPA's inadequate assessment of the health risks of formaldehyde. Evaluations of other

to the NAS for review (see go.nature.com/xnieqv). But the problems go deeper than the IRIS process.

Two main challenges render the EPA's risk assessments inadequate for decision-making. First, they take years or even decades to conclude, meaning that many chemicals have never been examined. Second, their scientific credibility is often challenged. Peer reviewers have questioned the EPA's selective use of data and some assumptions it has made to plug gaps in the scientific evidence. The NAS has recommended that the EPA better justify and quantify its risk-assessment assumptions.

As scientists who have served at the EPA (G.M.G.) and participated in NAS reviews (J.T.C.), we believe that more is needed. The agency needs to fundamentally alter its approach to risk evaluation. First, it should offer faster summaries for more chemicals. Rough-and-ready estimates are often sufficient for policy-making, and are better than nothing. IRIS should include information from private groups and other governments, and apply available techniques for calculating the risks of chemicals for which there are little data. Second, the EPA needs to acknowledge that its risk estimates are uncertain by reporting a range of plausible values, not just those that support its science-policy goals.

ROOTED IN THE PAST

Attitudes towards environmental regulation have changed since the agency was founded in 1970. Less than a decade after Rachel Carson exposed the environmental damage caused by the pesticide DDT in her 1962 book *Silent Spring*, Americans wanting "freedom from risk"[1] embraced government protection.

The EPA successfully addressed health threats posed by high-profile pollutants. A ban on leaded petrol spearheaded by the EPA in 1973 helped to reduce the level of lead in children's blood by nearly an order of magnitude in the decades that followed. Other agency regulations introduced in the early 1970s cut by half the levels of air pollutants such as sulfur dioxide and carbon monoxide.

By the mid-1990s, the most glaring environmental problems had been dramatically

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Path Forward

- Develop repositories of points of departure (PODs) - toxicologic values like $BMDL_{10}$ - for many chemicals
  - Based on data when available
  - Based on empirical relationships when not
  - Reflect uncertainty depending on amount of data
- These PODs can serve as starting point for risk-based decisions
  - Calculate RfD or VSD like values as with MCHM
  - Use Margin of Exposure approach?

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The Margin of Exposure (MOE)

$$\frac{\text{RfV}}{\text{Exposure}} = \text{MOE}$$

- Reference Value (RfV) is a point of departure (POD) from toxicologic or epidemiologic data
  - No Observed Adverse Effect Level
  - Benchmark Dose (or bound)
- Exposure can be measured or modeled – reflect variability
- More transparent than RfD like approaches – currently used in Canada, Europe, Australia and EPA OPP

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Challenges to Developing "Rough and Ready" Risk Values

- Need more research on empirical relationships to develop PODs for data-sparse chemicals
- Relationships may be biased by the aggressive interpretation of data in existing risk values
- How to quantitatively reflect the uncertainty due to different amounts of toxicity testing

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Challenges to Using "Rough and Ready" Risk Values

- Estimating exposures
- Getting comfortable using less than complete information to make decisions – although we do it in other settings
- Communicating the uncertainty we know exists
- An environment that is not good at updating decisions with new information
- I am sure you can think of many others

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Getting to R&R Risk Assessment

- Focus on quantitative – just prevent adverse effects
  - Endpoints don't predict anyway
  - Tox 21?

- Borrow knowledge from well studied chemicals – refine empirical relationships and QSARS and find new approaches

- Learn to live with uncertainty – better being able to make risk-based decisions about more chemicals rather than fewer – value of information guides new testing

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Summary

- We have to remember that risk assessments are not pursuits of scientific "truth" – they are tools to help inform decisions
- We can make quantitative statements about the potential risk of chemicals (with varying degrees of uncertainty) with widely ranging amounts of data
- Saying "we don't know" is both scientifically unsupportable and damages confidence in both government and industry
- Let's reinvigorate chemical risk management by developing and sharing more risk information!

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Thank You!